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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,436	09/06/2005	Silvio Aime	57708/380	7608

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
04/28/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

klpatent@kramerlevin.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,436	AIME ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/12/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,7 and 12-16* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,7,11,12,13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 2/12/2010, in reply to the Office Action mailed 9/15/2010, is acknowledged and has been entered. Claims 1, 3, 6, 7 and 12-16 are pending, of which claims 14 and 15 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claim 1 has been amended. Claim 16 is newly added. Claims 1, 3, 6, 7, 12, 13 and 16 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments have been fully considered but they are moot in view of new grounds for rejection, necessitated by claim amendment.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 6, 7, 12, 13 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a method of cellular labeling, including step (c) which includes degrading insoluble

particles by specific enzymes in the environment surrounding the insoluble particles so as to release single units of paramagnetic chelate and wherein a specific enzyme is selected from the group consisting of beta-galactosidase, esterase, proteinase, enzymes and lipase. The claim is confusing because it recites within a markush group drawn to "specific enzymes" such as esterase, lipase, etc., that "enzymes" are included in the group of "specific enzymes." However, "enzymes" is inclusive of all enzymes, not any specific enzyme. Therefore, the recitation of "enzymes" within a limited group of "specific enzymes" does not clearly define the scope of the claims. As such, the metes and bounds of the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 6, 12, 13 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Kabalka (*Mag. Res. in Medicine*, 1991, 19, p. 406-415).

Kabalka discloses gadolinium-labeled liposomes containing various amphiphilic Gd-DTPA derivatives as targeted MRI contrast enhancement agents for the liver. DTPA-SE is prepared by conjugation of stearyl alcohol to DTPA via an ester bond and DTPA-ST is prepared by conjugation of octadecanethiol (see Figure 1, page 407-8).

Liposomes were formed mixing Gd-DTPA, egg phosphatidylcholine, and cholesterol, and were then dried, vacuum desiccated and resuspended in phosphate buffered saline. The suspensions were sonicated to produce the desired small unilamellar vessicles with an average diameter of 0.05 micrometer (page 409). Coronal T1-weighted spin-echo images were obtained prior to and one hour after injection of various GLL agents (page 410). After one hour at least a portion of the Gd-DTPA-SE and Gd-DTPA-ST contrast agents degrade to small-molecular weight fractions (see Table 1). Magnetic resonance imaging experiments were performed utilizing the various GLL agents to determine if they provide visual contrast enhancement of the liver on a T1-weighted image. The diester and dithioester complexes resulted in 97 and 99% enhancements (page 411). The ester bond is readily cleared by the lysosomal esterases, once the DLL enters the cells via an endocytosis pathway. The expected degredation product is Gd-DTPA (page 413). See also page 414, the transfer of the agent to serum proteins and/or metabolism of the agent to some small-molecular-weight compounds was detected. The liposomes containing paramagnetic amphiphilic agents significantly enhance the MR signal intensity in T1-weighted MRI, and appear to be suitable contrast agents for enhancement of organs such as the liver, spleen, bone marrow, and other organs rich in macrophage (i.e. phagocytotic cells) activity.

Therefore, Kabalka meets the instant claim limitations of a) exposing insoluble particles comprising a gadolinium chelate having an aliphatic chain conjugated thereto and b) internalizing the particles inside the cells (i.e. via entrapment by the endocytosis pathway). Upon introduction into the cells, the particles would inherently be exposed to

enzymes to thereby degrade the particles, as Kabalka also teaches that the gadolinium-labeled liposomes containing the diester reagent are cleared from the liver rapidly as a consequence of the labile nature of the ester linkages due to esterases, and that at least some portion of the GLL agents have been degraded to small molecular weight fractions within an hour of administration, which is when imaging takes place, thus also meeting step d) of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 6, 7, 12, 13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kabalka (*Mag. Res. in Medicine*, 1991, 19, p. 406-415) in view of Ranney (US 5,155,215).

Kabalka discloses gadolinium-labeled liposomes containing various amphiphilic Gd-DTPA derivatives as targeted MRI contrast enhancement agents for the liver. DTPA-SE is prepared by conjugation of stearyl alcohol to DTPA via an ester bond and DTPA-ST is prepared by conjugation of octadecanethiol (see Figure 1, page 407-8). Liposomes were formed mixing Gd-DTPA, egg phosphatidylcholine, and cholesterol, and were then dried, vacuum desiccated and resuspended in phosphate buffered saline. The suspensions were sonicated to produce the desired small unilamellar

vessicles with an average diameter of 0.05 micrometer (page 409). Coronal T1-weighted spin-echo images were obtained prior to and one hour after injection of various GLL agents (page 410). After one hour at least a portion of the Gd-DTPA-SE and Gd-DTPA-ST contrast agents degrade to small-molecular weight fractions (see Table 1). Magnetic resonance imaging experiments were performed utilizing the various GLL agents to determine if they provide visual contrast enhancement of the liver on a T1-weighted image. The diester and dithioester complexes resulted in 97 and 99% enhancements (page 411). The ester bond is readily cleared by the lysosomal esterases, once the DLL enters the cells via an endocytosis pathway. The expected degredation product is Gd-DTPA (page 413). See also page 414, the transfer of the agent to serum proteins and/or metabolism of the agent to some small-molecular-weight compounds was detected. The liposomes containing paramagnetic amphiphilic agents significantly enhance the MR signal intensity in T1-weighted MRI, and appear to be suitable contrast agents for enhancement of organs such as the liver, spleen, bone marrow, and other organs rich in macrophage (i.e. phagocytotic cells) activity.

Therefore, Kabalka meets the instant claim limitations of a) exposing insoluble particles comprising a gadolinium chelate having an aliphatic chain conjugated thereto and b) internalizing the particles inside the cells (i.e. via entrapment by the endocytosis pathway). Upon introduction into the cells, the particles would inherently be exposed to enzymes to thereby degrade the particles, as Kabalka also teaches that the gadolinium-labeled liposomes containing the diester reagent are cleared from the liver rapidly as a consequence of the labile nature of the ester linkages due to esterases, and that at

least some portion of the GLL agents have been degraded to small molecular weight fractions within an hour of administration, which is when imaging takes place, thus also meeting step d) of the instant claims.

Kabalka does not specifically recite manganese as a paramagnetic ion.

Ranney discloses that T1 and T2 times have reciprocal effects on image intensity. Intensity is increased by either shortening the T1 or lengthening the T2. Tissue contrast occurs naturally and is related to variations in the chemical environments around water protons (major contributor) and lipid protons (usually minor). Chemical agents have been used to enhance this natural contrast. The one most widely tested clinically is the paramagnetic metal ion, gadolinium. Although gadolinium shortens both the T1 and T2 times, at the low dose used for clinical imaging, the T1 effect generally predominates and the image becomes brighter. Also, the rf pulse sequence can be programmed to accentuate T1 changes and diminish those due to T2. Hence, "T1-weighted" enhancement can be achieved by selecting the most favorable Gd dose and pulse sequence (column 2, lines 25-45). Gadolinium and manganese are disclosed as paramagnetic ions for binding DTPA in MRI imaging (claim 9).

It would have been obvious to one of ordinary skill in the art at the time of the invention to perform the MRI diagnosis disclosed by Kabalka via T1 weighted sequences because Ranney teaches that such sequences lead to image enhancement in conjunction with gadolinium contrast agents. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute manganese as a

functional equivalent to gadolinium as paramagnetic ion for use in MRI disclosed by Kabalka. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (Mn and Gd) and their functions were known in the art at the time of the instant invention. For example, Ranney teaches either Mn or Gd for binding DTPA for MRI imaging (claim 9). One of ordinary skill in the art could have substituted one known paramagnetic ion for another, and the results of the substitution would have been predictable, that is successful MRI imaging.

With regard to claim 12, liposome components of Kabalka increase the lifetime of particles in blood.

With regard to claim 13, Ranney teaches the benefits of targeted imaging such as for uptake by receptors, see column 9, lines 60+.

With regard to claim 16, the endocytosis pathway disclosed by Kabalka is a class of phagocytic cells (i.e. cells with macrophagic activity, as claimed) that take up particular substances.

Claim Objections

Claim 1 is objected to because of the following informality. In line 12 of the claim, a period appears after lipase. Appropriate correction is required.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS